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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/975,776	10/10/2001	Zhiwei Jiang	22596-514 (CO-14)	9481

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EXAMINER	
KRASS, FREDERICK F	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/975,776	JIANG ET AL.	
	Examiner	Art Unit	
	Frederick F. Krass	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

ontinuation of Disposition of Claims: Claims pending in the application are 1,2,6,9,11,12,15,18,19,21,22,25,28,30-4,36,37,40,43,45-48,51,54,180,182-186 and 204-209.

ontinuation of Disposition of Claims: Claims rejected are 1,2,6,9,11,12,15,18,19,21,22,25,28,30-34,36,37,40,43,45-8,51,54,180,182-186 and 204-209.

Obviousness Rejection

Claims 1, 2, 6, 9, 11, 12, 15, 18, 19, 21, 22, 25, 28, 30-34, 36, 37, 40, 43, 45-48, 51, 54, 180, 182-186 and 204-209 were rejected under 35 U.S.C. 103(a) as being unpatentable over Pardee (WO 00/61142), taken in view of Bodor (USP 4,983,586).

This rejection is maintained.

The Reddy declaration has been fully considered, and many of its assertions have been restated in Applicant's argument section. The declaration is an opinion affidavit, however, and cannot be given the same weight as corresponding factual evidence.

Applicant argues that there is no suggestion or motivation to combine the primary and secondary reference teachings and that, since the primary reference teaches the solubilization of B-lapachone and taxol in lipidol and the utility of these formulations in treating cancer without toxic side-effects, the skilled artisan reading the primary reference would have no desire or incentive to make a modification to arrive at the claimed invention. In other words, the mere fact that the primary reference could be modified does not make the modification obvious; the examiner has instead improperly applied hindsight in combining the prior art teachings.

The examiner agrees with Applicant's statement of the law, but believes the instant facts provide sufficient direction to arrive at the claimed subject matter. The mere fact that one particular solution to the solubility problems associated with B-lapachone solubility has been found by the prior art (i.e. solubilization in lipidol) does not mean that the skilled artisan would be foreclosed from additional routine experimentation. As previously stated in the prior Office action, the secondary reference provides simple tests for determining the usefulness of hydroxypropyl-beta-cyclodextrin in solubilizing various poorly soluble drugs, including various antineoplastic agents. This is fully consistent with the state of the art. See for example the article by Stella et al, "Cyclodextrins : Their Future in Drug Formulation and Delivery", *Pharmaceutical Research*, vol. 14, No. 5, pp. 556-567 (1997), already of record. As stated in the passage spanning the righthand column of p. 556, to the first paragraph of page 557:

It might be argued that other techniques can achieve these same goals [increased solubility], so why use cyclodextrins? Most other excipients used to solubilize and stablize drugs do so because of changes in the bulk properties of the resultant solvent. For example, cosolvents like various alcohols and glycols will increase the solubility of a poorly water soluble drug in a non-linear fashion with respect to co-solvent concentration... [but] most drugs form 1:1 complexes with various cyclodextrins.

e also p. 557, at the first paragraph of the righthand column:

[These] simple calculations allow one to determine whether a particular solubility goal is potentially realizable using a cyclodextrin formulation without the need for unnecessary experimentation.

The motivation for carrying out this routine experimentation is also stated in the secondary erence. See for example col. 14, lines 20-29:

Numerous drugs suffer from problems associated with their lack of water solubility and/or lack of stability in water. These lipophilic and/or water-labile drugs cannot be practically formulated as aqueous parenteral solutions. Consequently, the drugs are either unavailable for injection at the present time, or they are available for injectable use only in combination with undesirable organic vehicles: Injection of such vehicles undesirable because of the systemic and local toxicity which can result.

Lipidol is an organic vehicle. So, even after having achieved solubility with lipidol, one would ntinue to be motivated by the desired to further optimize solubility while minimizing toxicity. Solubiliztion h hydroxypropyl-beta-cyclodextrin provides a ready means for doing so using merely routine perimentation, and it would have been obvious to have done such testing to take advantage of the pected linear kinetics and lowered toxicity associated therewith.

Applicant further argues that no reasonable expectation of success exists for combining the prior disclosures. Specifically:

1) the secondary reference teaches away from the instant inventions since it states that B-clodextrin is poorly soluble;

2) the secondary reference contemplates only nineteen specific antitumor agents, with the rking examples being limited only to methotrexate, chlorambucil and lomustine;

3) there are many water-insoluble, antineoplastic compounds that are not readily solubilized with droxypropyl-beta-cyclodextrin, e.g. taxol and etoposide;

4) the chemical structures of the compounds in the primary reference are much larger than the chemical structures of the compounds in the secondary reference, and one could not predict that larger molecules could be solubilized; and

5) unexpected results have been shown.

The examiner does not agree with arguments 1)-4). Specifically:

1) the prior art does fairly teach that hydroxypropyl-beta-cyclodextrin is water-soluble, and this is Applicant's preferred species; accordingly, the fact that a non-preferred species (B-cyclodextrin) might not work as well is not seen to be relevant;

2) Applicant's assertions notwithstanding, the secondary reference appears to contemplate at least 57 (col. 21, line 61 to col. 22, line 14), not nineteen, antitumor agents; furthermore, the fact that three specific species are used in the working examples is not evidence, in and of itself, of any limitations on the prior art teachings, because a patent is not limited to its working examples but instead must be considered for the entirety of what it discloses;

3) etoposide is one of the species contemplated by the secondary reference (col. 22, line 14), a teaching which directly conflicts with the assertions made in Applicant's declaration; such assertions do not override the prior art teaching since they are general in nature and opinion only, unsupported by specific factual corroboration; and

4) again contrary to Applicant's assertions, the secondary reference does in fact contemplate the use of very large chemical structures, e.g. antitumor agents such as doxorubicin (col. 22, line 11), as well as such non-chemotherapeutics as steroids.

Unexpected Results

The examiner does agree with argument "5)", i.e. that unexpected results may have been shown. But, while the examiner agrees with the argument generally, there are some discrepancies regarding various particulars.

The examiner does not agree that the linear relationship observed between solubility and increase in hydroxypropyl-beta-cyclodextrin concentration is unexpected. This in fact appears to be expected, as previously discussed with regard to the Stella et al article (p. 557).

The examiner does agree that improved stability for B-lapachone/hydroxypropyl-beta-cyclodextrin complexes would be unexpected. Stability problems due to photoreactivity would be particular to B-lapachone, and not the various other species suggested in the prior art, because the mechanism of degradation of B-lapchone involves a pecularity of its particular structure: photoreduction to a semi-reduced quinone radical (see page 25, lines 10-16 of Applicant's specification).

The results discussed in Applicant's specification at page 25, lines 1-9 are not probative, however, because no actual factual evidence is provided to support the conclusions made therein. Furthermore, the instant claims are not commensurate in scope with the evidence presented therein, assuming its probativeness for the sake of argument. Increased stability is observed only for complexes of hydroxypropyl-beta-cyclodextrin with B-lapachone. The instant claims are by contrast broadly drawn, inclusive not only of those particular complexes but of simple physical mixtures, as well as complexes of B-lapachone derivatives and analogs having different functionality from the parent compound. Additionally, the broad claims are inclusive of other B-cylodextrins, including B-cyclodextrin itself, which Applicant has argued the prior art says is not soluble.

Suggestions to Place Claims in Condition for Allowance

In order to place the claims in condition for allowance, the examiner recommends: 1) providing factual evidence, preferably in the form of a Rule 132 affidavit, supporting all conclusions concerning unexpected stability allegedly observed; and 2) limiting the claims to be commensurate in scope with such evidence of unexpected results. The best way to do this would be to use a functional limitation, in order to avoid reciting specific species. An example would be:

> A pharmaceutical composition comprising a therapeutically effective amount of B-lapachone, or a derivative or anlalog thereof, and a pharmaceutically acceptable

solubilizing carrier molecule, wherein said solublilizing carrier molecule is a beta-cyclodextrin, and wherein said composition contains no detectable amount of the reduced (hydroquinone) form of said B-lapachone, as measured by HPLC analysis, following five days storage at room temperature.

Action is Final

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frederick F. Krass whose telephone number is 571-272-0580. The examiner's schedule is as follows:

Monday: 10:30AM- 7PM;
Tuesday: 10:30AM - 7PM;
Wednesday: off;
Thursday: 10:30AM- 7PM; and
Friday: 10:30AM-7PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Frederick Krass
Primary Examiner
Art Unit 1614